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1. Farber NJ, Jordan ME, Silverstein J, Collier VU, Weiner J, Boyer EG. Primary care physicians' decisions about discharging patients from their practices. *J Gen Intern Med*. 2008;23(3):283-287.

2. Dale SB, Ghosh A, Peikes DN, et al. Two-year costs and quality in the Comprehensive Primary Care initiative. *N Engl J Med*. 2016;374(24):2345-2356.

3. Peikes D, Anglin G, Taylor EF, et al. *Evaluation of the Comprehensive Primary Care Initiative: Third Annual Report*. Princeton, NJ: Mathematica Policy Research; 2016.

4. Stokes T, Dixon-Woods M, McKinley RK. Ending the doctor-patient relationship in general practice: a proposed model. *Fam Pract*. 2004;21(5):507-514.

Heat-Not-Burn Tobacco Cigarettes: Smoke by Any Other Name

The tobacco industry's most recent response to the documented harms of cigarette smoking was to launch new heat-not-burn (HNB) tobacco cigarettes.[1] Philip Morris International (PMI) created IQOS (I-Quit-Ordinary-Smoking): disposable tobacco sticks soaked in propylene glycol, which are inserted in a holder in the HNB cigarette. The tobacco is heated with an electric blade at 350°C. The cigarettes are marketed by PMI as a "revolutionary technology that heats tobacco without burning it, giving you the true taste of tobacco, with no smoke, no ash and less smell."[2] In many countries, laws that protect people from passive smoke only apply to smoked tobacco products. Philip Morris International claims that IQOS releases no smoke because the tobacco does not combust and the tobacco leaves are only heated not burned. However, there can be smoke without fire. The harmful components of tobacco cigarette smoke are products of incomplete combustion (pyrolysis) and the degradation of tobacco cigarettes through heat (thermogenic degradation). Complete combustion occurs at a high temperature (>1300°C), higher than the heat generated by smoking a tobacco cigarette (<800°C). Typical markers of pyrolysis and thermogenic degradation of tobacco cigarettes are acetaldehyde, an irritant carcinogenic volatile organic compound, benzo[a]pyrene, a carcinogenic polycyclic aromatic hydrocarbon, and carbon monoxide.

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Pilot programs for IQOS began in 2014 in Japan and in 2015 in Switzerland and Italy. An internet survey in Japan published in 2015 suggested that younger individuals (15 to 39 years of age) were more likely to use IQOS, as were former smokers and current smokers.[3] Since 2016, a total of 19 countries have allowed the sale of IQOS cigarettes. In June 2016, data from PMI revealed that IQOS had captured 2.2% of the cigarette market in Japan. IQOS is not yet sold in the United States, but in December 2016, PMI submitted a modified risk tobacco product application to the US Food and Drug Administration. If successful, PMI will be less restricted in its marketing for the IQOS than for conventional tobacco cigarettes. Smokers and nonsmokers need accurate information about toxic compounds released in IQOS smoke. This information should come from sources independent of the tobacco industry, but the only analyses we found were from PMI and PMI competitors.[1]

Methods | We compared the contents of IQOS (IQOS Holder, IQOS Pocket Charger, Marlboro HeatSticks [regular], and Heets, Philipp Morris SA) smoke with the contents of conventional cigarettes (Lucky Strike Blue Lights). We used a smoking device designed and tested in our facility to capture the mainstream aerosol and developed to meet standards for common cigarettes and e-cigarettes.[4] We followed the International Organization for Standardization standards for puff volume (35 mL) at 2 puffs per minute, based on observation of IQOS smokers, who took a mean of 14 puffs during 5 to 6 minutes. We analyzed volatile organic compounds and nicotine by gas chromatography coupled to a flame ionization detector and polycyclic aromatic hydrocarbons using high-performance liquid chromatography coupled to a fluorescence detector, as previously described.[4] We trapped polycyclic aromatic hydrocarbons from IQOS cigarette smoke in a glass filter (Whatman 37 mm Ø GF/B) mounted in line with an XAD2 cartridge. For each sampling, 10 IQOS cigarettes were smoked. Each sampling support was desorbed in 10 mL of acetonitrile and sonicated for 1 hour. The eluate was evaporated in a vacuum concentrator (Speed Vac SC-200, ThermoFisher Scientific) set with 30 millibars and 27*g* until the residue was almost dry to prevent evaporation of the most volatile polycyclic aromatic hydrocarbons. The residue was filtered with polytetrafluoroethylene membrane (Acrodisc CR 13 mm, 0.45 µm, Pall Life Sciences) before it was analyzed with a high-performance liquid chromatography device (Ultimate 3000, ThermoFisher Scientific) equipped with a fluorescence detector (FLD-3000RS), UV detector (VWD-3000), and a separation column Nucleodur EC 150 × 3 mm C18 3 µm (Macherey-Nagel) under isocratic conditions (1.2 mL · min^{-1}). We injected 2 µL into the high-performance liquid chromatography chain; methanol/water (70/30) with acetonitrile was the eluent solvent at an initial ratio of 100% to 0% (4 minutes) and a linear gradient up to 100% acetonitrile (12 minutes). We did not analyze polycyclic aromatic hydrocarbons generated by conventional cigarettes and present the mean values in the 35 best-selling cigarettes brands in the United States, as reported by Vu et al.[5] We monitored the temperature near the heater blade inside the IQOS holder and the core of the conventional cigarette at a sampling rate of 3 Hz with a type k thermocouple.

Results | Volatile organic compounds, polycyclic aromatic hydrocarbons, and carbon monoxide were present in IQOS smoke (**Table**). The temperature of the IQOS was lower (330°C) than the conventional cigarette (684°C).[5] The IQOS smoke had 84% of the nicotine found in conventional cigarette smoke.

Discussion | The smoke released by IQOS contains elements from pyrolysis and thermogenic degradation that are the same harmful constituents of conventional tobacco cigarette smoke. International experts were invited by PMI to describe the IQOS aerosol; one expert claims that "less than 2% by weight of the aerosol components may derive from the pyrolysis of the tobacco substrate which would not be sufficient to characterize the aerosol as 'smoke.'"[6(p 2)] In contrast, our analyses reveal that advertising slogans such as "heat-not-burn" are

Table. Concentrations of 8 Volatile Organic Compounds, 16 Polycyclic Aromatic Hydrocarbons, 3 Inorganic Compounds, and Nicotine in Mainstream Aerosol and Temperature of the HNB IQOS Cigarette and Conventional Cigarettes

Analyzed Compound	HNB Cigarette		Conventional Cigarette		Proportion of the Chemical in HNB and Conventional Cigarettes, %
	Amount, Mean (SD)	No. of Replications for Each Assay	Amount, Mean (SD)	No. of Replications for Each Assay	
Volatile organic compounds, µg per cigarette[a]					
Acetaldehyde	133 (35)	5	610[b]	1	22
Acetone	12.0 (12.9)	5	95.5 (13.5)	2	13
Acroleine	0.9 (0.6)	2	1.1	1	82
Benzaldehyde	1.2 (1.4)	5	2.4 (2.6)	2	50
Crotonaldehyde	0.7 (0.9)	5	17.4	1	4
Formaldehyde	3.2 (2.7)	5	4.3 (0.4)	2	74
Isovaleraldehyde	3.5 (3.1)	5	8.5 (10.8)	2	41
Propionaldehyde	7.8 (4.3)	5	29.6 (36.6)	2	26
Polycyclic aromatic hydrocarbons, ng per cigarette[c]					
Naphthalene	1.6 (0.5)	4	1105 (269)	7	0.1
Acenaphthylene	1.9 (0.6)	4	235 (39)	7	0.8
Acenaphthene	145 (54)	4	49 (9)	7	295
Fluorene	1.5 (0.6)	4	371 (56)	7	0.4
Anthracene	0.3 (0.1)	4	130 (18)	7	0.2
Phenanthrene	2.0 (0.2)	4	292 (44)	7	0.7
Fluoranthene	7.3 (1.1)	4	123 (18)	7	6
Pyrene	6.4 (1.1)	4	89 (15)	7	7
Benz[a]anthracene	1.8 (0.4)	4	33 (4.2)	7	6
Chrysene	1.5 (0.3)	4	48 (6.2)	7	3
Benzo[b]fluoranthene	0.5 (0.2)	4	24 (2.9)	7	2
Benzo[k]fluoranthene	0.4 (0.2)	4	4.3 (2.8)	7	9
Benzo[a]pyrene	0.8 (0.1)	4	20 (2.9)	7	4
Indeno[1,2,3-cd]pyrene	ND	4	NA	NA	NA
Benzo[ghi]perylene	ND	4	NA	NA	NA
Dibenzo[a,h]anthracene	ND	4	NA	NA	NA
Inorganics, ppm in the mainstream smoke[d]					
Carbon dioxide	3057 (532)	5	>9000	3	NA
Carbon monoxide	328 (76)	5	>2000	3	NA
Nitric oxide	5.5 (1.5)	5	89.4 (71.6)	3	6
Other measures					
Nicotine, µg per cigarette[a]	301 (213)	4	361	1	84
Temperature, °C	330 (10)	2	684 (197)	1	NA
Puff total count	12.6 (2.4)	32	13.3 (3.1)	6	NA

Abbreviations: HNB, heat-not-burn; NA, not analyzed; ND, not detected.

[a] We applied the methods described previously in Varlet et al[4] to analyze volatile organic compounds and nicotine.

[b] Because there was only 1 replication, no SD can be computed.

[c] We present values reported from Vu et al[5] for the ISO smoking regimen and for a mean of the 35 top-selling US cigarette brands.

[d] Carbon dioxide was measured with a Testo 535 (Testo), and carbon monoxide and nitric oxide were measured with a Pac 7000 that detected carbon monoxide (Draeger). The apparatus measured the smoke when it was released from the syringe pump.

no substitute for science. Dancing around the definition of smoke to avoid indoor-smoking bans is unethical. Principle 1 for implementing article 8 of the World Health Organization convention on tobacco control highlights that we should reject ideas that there is a threshold value for toxic effects from second-hand smoke. Independent studies should further evaluate the health effects of the IQOS. In the meantime, heated tobacco products such as IQOS should fall under the same indoor-smoking bans as for conventional tobacco cigarettes.

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Accepted for Publication: March 15, 2017.

Published Online: May 22, 2017. doi:10.1001/jamainternmed.2017.1419

Author Contributions: Drs Auer and Berthet had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Statistical analysis: Concha-Lozano.
Obtained funding: Cornuz, Berthet.
Administrative, technical, or material support: Concha-Lozano, Berthet

Conflict of Interest Disclosures: None reported.

1. Schaller J-P, Keller D, Poget L, et al. Evaluation of the Tobacco Heating System 2.2, part 2: chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol. *Regul Toxicol Pharmacol*. 2016;81(suppl 2):S27-S47.

2. IQOS. About IQOS. https://www.iqos.co.uk/about-iqos.html. Accessed March 6, 2017.

3. Tabuchi T, Kiyohara K, Hoshino T, Bekki K, Inaba Y, Kunugita N. Awareness and use of electronic cigarettes and heat-not-burn tobacco products in Japan. *Addiction*. 2016;111(4):706-713.

4. Varlet V, Concha-Lozano N, Berthet A, et al. Drug vaping applied to cannabis: is "Cannavaping" a therapeutic alternative to marijuana? *Sci Rep*. 2016;6:25599.

5. Vu AT, Taylor KM, Holman MR, Ding YS, Hearn B, Watson CH. Polycyclic aromatic hydrocarbons in the mainstream smoke of popular U.S. cigarettes. *Chem Res Toxicol*. 2015;28(8):1616-1626.

6. Cozzani V. Expert Opinion on Smoke. https://www.pmiscience.com/sites/default/files/executive_summary_of_prof_cozzanis_report.pdf. Accessed November 29, 2016.

Editor's Note

No Smoke—Just Cancer-Causing Chemicals

Heat-not-burn tobacco products are for sale around the world. Although they are not yet on the market in the United States, Phillip Morris International has applied to the US Food and Drug Administration (FDA) to sell these products. These products threaten the progress that has been made on decreasing the harms of second-hand smoke because existing bans may not apply to these heat-not-burn products. However, as convincingly reported by Auer and colleagues,[1] although these products may or may not produce smoke, they release cancer-causing chemicals. As shown in their table, heat-not-burn cigarettes release similar levels of many volatile organic compounds and nicotine as conventional cigarettes and higher levels of the polycyclic aromatic hydrocarbon acenaphthene than conventional cigarettes. They are bad for health because they release cancer-causing chemicals, and I hope the FDA will not approve them for that important reason. If the FDA does approve the sale of these products, existing smoking bans should be amended to include these products.

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Conflict of Interest Disclosures: None reported.

1. Auer R, Concha-Lozano N, Jacot-Sadowski I, Cornuz J, Berthet A. Heat-not-burn tobacco cigarettes: smoke by any other name [published online July 1, 2017]. *JAMA Intern Med*. doi:10.1001/jamainternmed.2017.1419

COMMENT & RESPONSE

Neuroleptics for Delirium: More Research Is Needed

To the Editor We read with interest the Original Investigation in a recent issue of *JAMA Internal Medicine* by Agar et al[1] on the management of delirium in the palliative care setting. Delirium is one of the most common and disturbing syndromes at the end of life,[2] and there are few well-designed studies to inform practice.[3] Because data from geriatrics and other populations cannot be extrapolated to the palliative care setting, this important study[1] provides unique insights into the role of haloperidol and risperidone compared with placebo; however, several issues regarding the study design complicate its interpretation.

We wonder if the composite subscore of the Nursing Delirium Screening Scale (NuDesc) is an appropriate primary outcome. Although NuDesc has been validated, this subscore has not been studied before, and the minimal clinical important difference has not been defined. While haloperidol and risperidone arms were associated with statistically significant worse NuDesc subscores, the magnitude of change may not be clinically meaningful based on the investigator-defined cutoff (<1 point).

If haloperidol and risperidone were indeed ineffective, could the low medication doses explain it? In our acute palliative care unit, daily haloperidol doses of more than 8 mg were often needed for patients who were agitated.[4,5] We are also curious that despite the low dose and short duration of neuroleptic use, Agar et al[1] reported shortened survival with risperidone. Given the large number of secondary outcomes, these findings should be considered as hypothesis-generating, and further studies are needed.

These are confusing times. Clinicians caring for patients with agitated delirium have to grapple with the dilemma of uncertain benefits and potential risks with neuroleptics for a distressing condition for which few other proven interventions are available. While identification of reversible causes and nonpharmacological measures seem intuitive, these interventions need to be standardized and tested formally in the palliative care setting in which delirium is often severe, progressive, and irreversible. For the large portion of patients who do not respond to these measures, neuroleptics may still have a role for refractory agitation. This study also reopens the debate on whether benzodiazepines alone should be considered for delirium. Given this is a single study enrolling predominantly patients with mild delirium (median Memorial Delirium Assessment Scale score, 13-15), it is premature to close the chapter on neuroleptics in palliative care as suggested by the authors and the accompanying editorial.[1] Instead, this study highlights the tremendous opportunities